

UNCLASSIFIED

Defense Technical Information Center
Compilation Part Notice

ADP011048

TITLE: Melatonin and Aircrew: Is an Operational Use Recommended?

DISTRIBUTION: Approved for public release, distribution unlimited

This paper is part of the following report:

TITLE: Medication for Military Aircrew: Current Use, Issues, and Strategies for Expanded Options [les medicaments pour les equipaes militaires: Consommation actuelle, questions et strategies pour des options elargies]

To order the complete compilation report, use: ADA395446

The component part is provided here to allow users access to individually authored sections of proceedings, annals, symposia, etc. However, the component should be considered within the context of the overall compilation report and not as a stand-alone technical report.

The following component part numbers comprise the compilation report:

ADP011041 thru ADP011058

UNCLASSIFIED

Melatonin and Aircrew: Is an Operational Use Recommended?

Philippe Doireau

Service de Médecine Aéronautique et de Pathologies Cardiovasculaires
HIA Percy, 101 av. H. Barbusse, 92141 Clamart, France

Jean-François Paris, M.D.

Jean Pierre Gourbat, M.D.

Service de Médecine-Cardiologie
Centre Principal d'Expertise Médicale du Personnel Navigant
101 Avenue Henri Barbusse, 92141 CLAMART Cedex, France

RESUME

Le syndrome de désynchronisation induit par le franchissement répété de fuseaux horaires ou «jet lag» induit des enjeux non négligeables en terme de performance et de sécurité des vols lors de déploiements rapides de forces. Si certaines solutions physiques et pharmacologiques ont été proposées, l'utilisation de la mélatonine pourrait à terme se concevoir. Après une revue de la littérature, les auteurs mettent en exergue les problèmes pratiques encore non résolus liés à l'utilisation de cette substance. L'absence de certitudes scientifiques rend actuellement nécessaire une certaine prudence avant son emploi dans le personnel navigant.

SUMMARY

The time difference-related desynchronization syndrome commonly called "jet lag" raises many issues in terms of performance and flight safety during rapid military deployments. Of several physical and pharmacological solutions recently proposed, the use of melatonin is generally considered to be a promising coping strategy. In this literature review, the authors have highlighted practical unsolved considerations in the use of melatonin. A conservative attitude, especially about its use in aircrew, currently remains necessary because of the lack of scientific certainties.

JET LAG: A SHORT REVIEW

The time difference-related desynchronization syndrome commonly called "jet lag" is an experience shared by millions of international travelers each year, as well as by the crews

manning the aircraft transporting them. In the military field, jet lag may impair the performance of military personnel involved in a rapid overseas deployment. The pathophysiology of jet lag is not completely elucidated. Given that several time zones are crossed very quickly, local time upon arrival is not the same as local time at the point of departure, a calculation to which journey time must be added. At a physiologic level, the time difference induces a state of desynchrony in the individual temporal structure which leads to various symptoms.^{51,33,24,16} The symptoms of jet lag are represented above all by disruption of the sleep-wake cycle, with nocturnal insomnia and diurnal drowsiness.^{33,44,45} Other clinical manifestations can be associated with it, such as a sensation of unease, asthenia, irritability, diminished physical^{19,20,39} and cognitive performance,⁷ anxiety, the appearance of depressive phenomena, and finally digestive disorders.^{52,8} These symptoms typically appear after a flight crossing five or more time zones, and are all the more pronounced the greater the number of zones crossed. The direction of the flight is significant; an eastward flight, which demands an advance in the sleep phase, is less well tolerated than a westward flight, which demands a delay in phase. Overall resynchronization capacity is estimated at 1 hour per day for an eastward journey, compared with 1 hour and a half per day for a westward journey.^{21,8} Individual factors are also influential, as certain personalities, such as an "evening person" or "owl," rather than a "morning person" or "lark,"¹⁸ as well as youth, favor rapid resynchronization.³¹ Following arrival, the conflict between the subject's internal circadian rhythm and the action of external synchronizers in the environment fades progressively, as natural (light/dark cues) and social (alternation of work/rest) synchronizers reset the various biological rhythms

more or less quickly. Consequently, various physiological strategies, possibly combined together, have been proposed to cope with jet lag, with physical exercise, bright light exposure, and modification of dietary intake being the most often cited. Physical exercise generally has a positive impact,⁴⁶ but the effect of bright light has not convincingly been demonstrated,⁴² and there exists no controlled study using dietary adjustment. Furthermore, the application of such strategies is not always compatible with social activities. Gradually modifying bedtime before departure is also not advisable because it induces symptoms of jet lag before the journey.

PHARMACOLOGIC MANAGEMENT OF JET LAG

Any treatment able to alleviate jet lag and accelerate the resynchronization of biological rhythms would be of interest in terms of operational efficiency for the military, both for the sense of well-being of aircrew and travelers, and also in view of flight safety. Existing treatments appear to alleviate the symptoms of jet lag with varying degrees of success. Hypnotic drugs may be of benefit to avoid sleep disturbance. Benzodiazepines in particular have been extensively studied. They induce sleep and offer the individual a subjectively better night, but possible side effects like daytime drowsiness, lowered performance and anterograde amnesia are concerning. By taking the duration of action into account, the physician may be able to use such drugs under certain circumstances.⁴⁹ Among the benzodiazepines, temazepam has received the most attention and seen the widest operational use.³² With a very short half life, zolpidem seems to have fewer side effects than benzodiazepines, and has been proposed to induce anticipatory or recovery sleep in aircrew.⁴⁷

Interestingly, perhaps due to their restricted availability in many countries, stimulants have not been studied for jet lag therapy. Nevertheless, either amphetamines or modafinil could be of interest to sustain vigilance after arrival and speed up resynchronization.²² Caffeine tablets are generally too short-acting to sustain vigilance for the entire diurnal period; slow-release caffeine offers a valuable alternative, but remains to be tested in this context.²³

MELATONIN

Main Characteristics

Melatonin is a natural hormone, derived from serotonin, which is secreted by the pineal gland primarily during the hours of darkness. Melatonin is able to shift various biological rhythms by giving the internal clock an endogenous signal reflecting light/dark alternation in the environment;²⁵ such a property is known as chronobiotic.¹⁴ Melatonin, the secretion of which is stimulated by darkness and inhibited by daylight, permits adjustment of the 25 hour periodicity characteristic of the suprachiasmatic nucleus to one of 24 hours. Thus, the pineal gland resynchronizes the master clock in the suprachiasmatic nucleus (SCN) by means of melatonin. The circadian rhythmicity of various hormonal (e.g., cortisol), vegetative (e.g., core temperature, sleep-wake cycle) and behavioral (e.g., activity) rhythms is then strengthened.¹⁰

The effects of melatonin are widespread but incompletely understood.¹ The secretion of melatonin at night reinforces the nadir of temperature³⁸ and coincides with sleep and low levels of cortisol secretion. It is clear, however, that melatonin is not the "sleep hormone," given that its secretion occurs at night even in nocturnal species such as rodents. Melatonin secretion begins at around 9-10 PM, reaches a peak around 3 AM (50-70 pg.ml⁻¹ in plasma), and disappears at around 7-9 AM. The melatonin secretion profile varies from one individual to another, but is relatively constant within the same individual from night to night. The melatonin rhythm is not very sensitive to masking effects, being little influenced by external stimuli save that engendered by light. The half-life of orally administered melatonin is 35 to 50 minutes; its major (90%) hepatic metabolite is 6-sulphatoxymelatonin which, measured in the urine, provides a reliable method to assess the quantity of melatonin secretion in a noninvasive way.

Toxicologic studies in rodent models have been unable to determine an LD₅₀. In the absence of toxicity, exogenous melatonin administration at pharmacological doses has been carried out in humans in order to better understand its physiologic role and to determine its potential therapeutic use in circadian rhythm disorders. The power of exogenous melatonin resides in its capacity to modify

endogenous secretion in accordance with a phase-response curve in a dose-dependent manner,^{25,15} and not by conventional feedback. Thus a dose of melatonin taken in the afternoon or evening brings about a phase advance - the peak of endogenous melatonin appears earlier and circadian rhythms are brought forward. A dose given in the morning or at midday entails a phase delay - the peak of endogenous melatonin appears later and circadian rhythms are postponed.²⁷ The strength of this chronobiotic effect is still under debate and it could be less important than previously assessed.⁴¹ This point needs to be clarified in the future, since it clearly serves as the physiologic rationale for the potential use of melatonin as a jet lag therapy.

In the clinical field, melatonin has shown some success in delayed sleep phase syndrome, insomnia in the elderly, and blindness-related circadian disorders,⁴⁸ although the timing of administration needs to be optimized.²⁶

Melatonin And Jet lag

The use of melatonin in preventing and treating jet lag has been investigated by relatively few controlled studies,^{2,3,4,10,13,28,34,35,36,37} one of which was carried out under simulated conditions.⁴³ To our knowledge, the use of a melatonin agonist in the context of a jet lag protocol has not been published to date. The dose of melatonin used in these studies ranges from 5 to 10 mg, with 5 mg being the most commonly used. Administration of the agent varies between studies; the duration of treatment ranges between 3 and 9 days, beginning 3 days before the flight at the earliest, and the day after the flight at the latest, and ending 3 to 4, or even 5 to 7, days after the flight. In fact, prophylactic administration which takes place too prematurely may lead to drowsiness due to melatonin's sedative properties.⁵ The time when the treatment is taken must be regular, in that before, during, and after the journey, it must correspond to bedtime in the country of destination. For an eastward flight, preventive doses will be taken in the late afternoon to achieve pre-synchronization, i.e., to induce a phase advance. Upon arrival, the treatment is taken at bedtime. Theoretically, a pre/post flight administration should be more efficient than a simplified protocol of post flight administration only, but study results remain inconclusive on this point. A significant alleviation of jet lag symptoms through the use of melatonin has been demonstrated in the course of these studies, but assessments were almost always

subjective, using a sleep log, and visual analogue scales for jet lag tolerance, alertness, asthenia, and mood. The most objective studies, using actigraphy and/or performance tests,^{33,14} demonstrated an increase in sleep duration and a faster resynchronization of subjects' rhythms (sleep-wake cycle, endogenous melatonin rhythm, temperature rhythm) when using melatonin compared to placebo. Cognitive and psychomotor performance of treated subjects were shown to be better than those of subjects receiving placebo.¹⁴ Physical strength has never been evaluated in any study.

It should be noted that a small percentage (~10%) of subjects feel "worse" with melatonin, probably due to an administration timetable that is poorly adapted to the circadian clock of these subjects.^{4,36} Interindividual variations in the flexibility of temporal organization may also account for such results. Ideally, physicians should assess the potential impact before giving any chronobiotic drug to a subject.⁶ The majority of subjects experienced no side effects during these studies. However, drowsiness may appear 30 minutes after taking 5 mg of melatonin and may last approximately 1 hour.³ According to Arendt, only higher doses of 50 and 80 mg of melatonin have demonstrated a clear hypnotic effect,¹ although Sack argues that there is a dose-response effect on sleep starting with lower supraphysiologic doses.⁴⁰ Dollins et al. agree that supraphysiologic levels of urinary 6-sulfatoxymelatonin are associated with cognitive performance impairment.¹⁷ In jet lag studies, other minor side effects like nausea and headache have also been observed.⁴ Recently, irregular sleep-wake cycle related to more prolonged melatonin intake has been described by Middleton et al.² Comperatore et al have tried to address the question of the grounding time of personnel after melatonin administration, and have noted that this grounding period should not exceed the time necessary for spontaneous resynchronization. They advised a 16 to 24 hour grounding time after a single administration of 10 mg at 2300 hours. A recovery sleep may shorten this duration.

CONCLUSION

The previous cited studies have shown that melatonin likely has an impact on jet lag symptoms, and demonstrate the presence of a chronobiotic effect, albeit a weak one. The potential usefulness of a compound like melatonin for military

deployments is obvious. Scientific literature has not yet provided clear answers to a number of practical considerations that need to be clarified:

- Administration timetable is still uncertain.
- Optimal dose is still to be identified; lower doses than those previously tested may be of interest, perhaps 3 to 5 mg maximum.
- Benefits in terms of sleep-wake resynchronization and performance sustainment should be confirmed.
- Side effects, especially transitory drowsiness, need to be clearly assessed, particularly if one is considering drug administration to active aircrew, and not just to passengers during the flight.

Future collaborative studies should address these questions before the optimal use of melatonin in the context of military operations can be ascertained.

REFERENCES

1. Arendt J. *Melatonin and the mammalian pineal gland*. Chapman & Hall Ed 1995.
2. Arendt J. Melatonin in humans: jet lag and after. *Advances in pineal research*. Josephine Arendt and Paul Pevet (Eds) John Libbey and Co Ltd, 299:302, 1991.
3. Arendt J, Aldhous M. Further evaluation of the treatment of jet lag by melatonin: a double blind crossover study. *Ann Rev Chronopharmacol* 1988; 5:53-5.
4. Arendt J, Aldhous M, English J, Marks V, Arendt JH. Some effects of jet lag and their alleviation by melatonin. *Ergonomics* 1987;30:1379-3.
5. Arendt J, Bordely AA, Francy C, Wright J. The effect of chronic small doses of melatonin given in the late afternoon on fatigue in man: a preliminary study. *Neuroscience Letters* 1984;45:317-21.
6. Ashkenazi IE, Reinberg AE, Motohashi Y. Interindividual differences in the flexibility of human temporal organisation: pertinence to jet lag and shiftwork. *Chronobiol Int* Mar 1997;14(2): 109-13.
7. Beh HC. Mental performance of air crew following layovers on transzonal flights. *Ergonomics* 1991;34(2):123-35.
8. Billiard M. *Le sommeil normal et pathologique: troubles du sommeil et de l'éveil*. Edition MASSON; 1994.
9. Brown GM, Vos EC. Melatonin and its role in circadian rhythm disruption. NATO - RTA - AMP Meeting, 29 Sep-3 Oct 1997, Rotterdam.
10. Claustat B, Brun J, David M, Sassolas G, Chazot G. Melatonin and jet lag: confirmatory result using a simplified protocol. *Biol Psychiatry* 1992;32:705-11.
11. Claustat B, Geoffriau J, Brun J. La melatonine: de l'hormone au médicament? *Pathologie et Biologie* 1996;44:645-53.
12. Comperatore CA, Kirby AW, Clayton M, Rivera P, Bey-Wright R, Wright D. Aviator's grounding time after melatonin administration during rapid deployment missions. NATO - RTA - AMP Meeting, 29 Sep-3 Oct 1997, Rotterdam.
13. Comperatore CA, Lieberman HR, Kirby AW, Adams B, Crowley JS. Melatonin efficacy in aviation missions requiring rapid deployment and night operations. *Aviat Space Environ Med* 1996; 67:520-4.
14. Dawson D, Armstrong SM. Chronobiotics – drugs that shift rhythms. *Pharmacol Ther* 1996; 69:15-36.
15. Deacon S, Arendt J. Melatonin-induced temperature suppression and its acute phase-shifting effects correlate in dose-dependent manner in human. *Brain Research* 1995;688:77-85.
16. Dement WC, Seidel WF, Cohen SA, Bliwise NG, Carskadon MA. Sleep and wakefulness in aircrew before and after transoceanic flights. *Aviat Space Environ Med* 1986;57(12):B14-28.
17. Dollins AB, Lynch HJ, Wurtman RJ, Deng MH, Kischka KU, Gleason RE, Lieberman HR. Pharmacological daytime doses of melatonin on human mood and performance. *Psychopharmacol* 1993;112:490-6.
18. Haffen E, Denis JB, Lagarde D. Personality and resistance to sleep deprivation. *Proceedings of the 3rd International Meeting on Sleep Disorders*, Bordeaux; 17-18 April 1997, p. 115.

19. Hill DW, Hill CM, Fields KL, Smith JC. Effects of jet lag on factors related to sport performance. *Can J Appl Physiol* 1993;18(1):91-103.
20. Jehue R, Street D, Huizenga R. Effect of time zone and game time changes on team performance: National Football League. *Med Sci Sports Exerc* 1993;25(1): 127-31.
21. Klein KE, Wegmann HM. Significance of circadian rhythms in aerospace operations. *NATO AGARDograph* 1980;247.
22. Lagarde D, Doireau P. Le decalage horaire. *Méd Trop (Mars)* 1997;57 bis:489-92.
23. Lagarde D, Louguet PH, Batejat D, Trocherie S, Chassard D, Thebault J, Chauffard F, Enslen M, Tachon P. Time release caffeine: an interesting substance against limited sleep deprivation and jet lag? 4th Congress of the Asian Sleep Research Society, Jerusalem; August 25-28, 1997.
24. Lagarde D. Décalage horaire: mettre les pendules à l'heure. *Le Concours Médical, Médecine interne*, 1995;16(12):117-42.
25. Lewy AJ, Ahmed S, Jackson JM, Sack RL. Melatonin shifts human circadian rhythms according to a phase-response curve. *Chronobiol Int* 1992;9:380-92.
26. Lewy AJ, Sack RL. Exogenous melatonin's phase-shifting effects on the endogenous melatonin profile in sighted humans: a brief review and critique of the literature. *J Biol Rhythms* 1997;12(6):588-94.
27. Lewy AJ, Sack RL, Blood ML, Bauer VK, Cutler NL, Thomas KH. Melatonin marks circadian phase position and resets the endogenous circadian pacemaker in humans. *Proc Symp Ciba Geigy*; 1994, p. 303-21.
28. Lino A, Silvy S, Condorelli L, Rusconi AC. Melatonin and jet lag: treatment schedule. *Biol Psychiatry* 1993;34:587.
29. Middleton BA, Stone BM, Arendt J. Melatonin and fragmented sleep patterns. *Lancet* 1996; 348(9026):551-2.
30. Moline ML, Pollack CP, Monk TH, Lester LS, Wagner DR, Zendell SM, Graeber RC, Salter CA, Hirsch E. Age-related differences in recovery from simulated jet lag. *Sleep* 1992;15(1):28-40.
31. Monk TH, Buysse DJ, Reynolds CF, Kupfer DJ. Inducing jet lag in older people: adjusting to a 6-hour phase advance in routine. *Exper Gerontol* 1993;28:119-33.
32. Nicholson AN, Stone BM. Sommeil et vigilance: manuel à l'usage des médecins de l'aéronautique. *NATO AGARDographie* N° 270, 1987.
33. Nicholson AN, Spencer MB, Pascoe PA, Stone BM, Roehrs T, Roth T. Sleep after transmeridian flights. *Lancet* 1986 Nov 22; 2(8517):1205-8.
34. Nickelsen T, Lang A, Bergau L. The effect of 6-, 9- and 11-hour time shifts on circadian rhythms: adaptation of sleep parameters and hormonal patterns following the intake of melatonin or placebo. *Advances in pineal research*. Josephine Arendt and Paul Pevet (Eds) John Libbey and Co Ltd. 1991;5:303-6.
35. Petrie K, Conaglen JV, Thompson L, Chamberlain K. Effect of melatonin on jet lag after long haul flights. *Br Med J* 1989;298:705-7.
36. Petrie K, Dawson AG, Thompson L, Brook R. A double-blind trial of melatonin as a treatment for jet lag in international cabin crew. *Biol Psychiatry* 1993; 33:526-30.
37. Petrie K, Dawson AG. Recent developments in the treatment of jet lag. *J Travel Med* 1994:79-83.
38. Reid K, Van Den Heuvel C, Dawson D. Daytime melatonin administration: effects on core temperature and sleep onset latency. *J Sleep Res* 1996;5:150-4.
39. Reilly T, Atkinson G, Waterhouse J. Travel fatigue and jet lag. *J Sports Sci* 1997;15(3):365-9.
40. Sack RL, Hughes RJ, Edgard DM, Lewy AJ. Sleep-promoting effect of melatonin: at what dose, in whom, under what conditions, and by what mechanisms? *Sleep* 1997;20(10):908-15.
41. Sack AJ, Lewy AJ. Melatonin as a chronobiotic: treatment of circadian desynchrony in night workers and the blind. *J Biol Rhythms* 1997;12(6):595-603.

42. Samel A, Wegmann HM. Bright light: a countermeasure for jet lag? *Chronobiol Int* 1997;14(2):173-83.
43. Samel A, Wegman HM, Vejdova HM, Maab H, Gundel A, Schutz M. Influence of melatonin treatment on human circadian rhythmicity before and after a simulated 9-hour time shift. *J Biol Rhythms* 1991;6:235-48.
44. Sasaki M, Kurosaki Y, Spinweber CL, Mori A, Endo S. Patterns of sleep-wakefulness before and after transmeridian flight in commercial airline pilots. *Aviat Space Environ Med* 1986;57(12):B29-42.
45. Sasaki M, Kurosaki Y, Spinweber CL, Graeber C, Takahashi T. Flight crew sleep during multiple layover polar flights. *Aviat Space Environ Med* 1993;64:641-7.
46. Shiota M, Sudou M, Ohshima M. Using outdoor exercise to decrease jet lag in airline crewmembers. *Aviat Space Environ Med* 1996;67:1155-60.
47. Sicard B, Trocherie S, Moreau J, Vieillefond H, Court L. Evaluation of zolpidem on alertness and psychomotor ability among aviation ground personnel and pilots. *Aviat Space Environ Med* 1993;64:371-5.
48. Skene DJ, Deacon S, Arendt J. Use of melatonin in circadian rhythm disorders and following phase shifts. *Acta Neurobiol Exp* 1996;56:359-62.
49. Stone B, Turner C. Promoting sleep in shift-workers and intercontinental travelers. *Chronobiol Int* 1997; 14(2):133-43.
50. Sugden G. Psychopharmacological effects of melatonin in mouse and rat. *Pharmacol Exp Ther* 1993; 227:587-91.
51. Waterhouse J, Reilly T, Atkinson G. Jet lag. *Lancet* 1997;350(9091):1611.
52. Winterburn S, Atkinson G, Waterhouse J, Reilly T. Towards Sydney 2000: monitoring jet lag in a national sports team. *Chronobiol Int* 1997;14(1):183.